REMARKS

Claims 1-16 and 33-34 are pending. Claims 1, 3, 4, 33 and 34 have been amended. Claim 2 has been cancelled. Claims 17-32 and 35-40 have been withdrawn. Withdrawn claim 30 has been amended consistent with the amendments made to the pending claims. Applicants reserve the right to rejoin the withdrawn claims upon a finding of allowance. No new matter has been added.

Claim 1 has been amended to recite "prostate specific membrane antigen" prior to the abbreviated language "PSMA". In addition, claim 1 has been amended to remove the word "to" prior to the phrase "thereby determining if a subject is at risk for prostate cancer recurrence". The amendments to claim 1 obviate the objections to the claims.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-16 and 33-34 are rejected under 35 U.S.C. §112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, claims 1-16 and 33-34 are rejected "because it is not clear which reference standard, as cited in claims 1, 3 is referred to, for use in the claimed method. Claims 1 and 3 have been amended to recite "a reference standard that is statistically significant between subjects having recurrence and subjects that do not have recurrence". The amendments to claims 1 and 3 obviate this rejection.

Claim 4 is further rejected as "indefinite, because it is not clear how the control subject is distinguished from the tested subject, because both were diagnosed with prostate cancer." Claim 4 has been amended to indicate that the control subject is a subject that has been diagnosed with prostate cancer and that does not have prostate cancer recurrence. The amendment to claim 4 obviates this rejection.

In addition, claims 33 and 34 are rejected "because the term 'higher' level of expression is a relative term". Claims 33 and 34 have been amended to recite "a subject that does not have a

statistically significant increase of PSMA expression as compared to the reference standard". The amendments to claims 33 and 34 obviate this rejection.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-16 and 33-34 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the written description requirement." According to the Office Action, "PSMA without being accompanied by a sequence identification number reasonably reads on a genus of variant transmembrane folate hydrolases." Specifically, page 6 of the Office Action states

> In this case, the specification does not describe PSMA protein in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide sufficient structure or common structure to support the broad breadth of the claimed genus. Nor is there any functional characteristic coupled with known or disclosed correlation between structure and function. Thus, the specification does not provide a description of PSMA protein, that would satisfy the standard as shown in the example of Enzo.
>
> The specification also fails to describe PSMA protein, by the standards shown in the example in Lilly.

Thus, the Office Action concludes at page 7, that "the specification does not provide an adequate written description of PSMA protein that is required to practice the claimed invention."

Applicants respectfully traverse this rejection. PSMA is not a new protein. Instead PSMA was a term used in the art at the time of filing to describe a known protein with a known amino acid sequence. The fact that the background of the invention section of the application provides that PSMA is "transmembrane folate hydrolase consisting of 750 amino acids and having a molecular weight of 110 kDa" does not change the meaning of that term. In fact, the background of the invention specifically recites references available at the time of filing that disclose the amino acid sequence of PSMA. Since PSMA had a known structure at the time of filing, there is no need to describe the sequence in the present application to satisfy the written description requirements.

The Office Action incorrectly cites the standards set forth in Lilly and Enzo for what is required to satisfy the written description requirement for the PSMA protein. Instead, the

appropriate standard is set forth in Capon v. Eshhar v. Dudas, 418 F. 3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005). Similar to the description of PSMA in the present application, the applications at issue in Capon disclosed known sequences by reference to their name. There was no disclosure in the applications at issue of the nucleic acid encoding or amino acid sequences of the claimed chimeric proteins. The Federal Circuit in Capon held that

> the Board's requirement that these sequences must be analyzed and reported in the specification does not add substantive description. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

In it's analysis, the Federal Circuit discussed the Lilly and Enzo cases cited by the Office Action and distinguished those cases from a scenario where the sequences in question were known in the art. The Federal Circuit stated that "none of the cases to which the Board attributed the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen or Enzo Biochem, require a re-description of what was already known." The Federal Circuit specifically distinguished Lilly and Enzo from the case where the sequence was known in the art, stating "In Lilly, ...the cDNA for human insulin had never been characterized. ...In Enzo Biochem, ... this court reaffirmed that a deposit of a physical sample may replace words when the description is beyond present scientific capability." Since the present application also discloses the name of a protein having a known amino acid sequence, it is clear that Applicants do not need to recite the amino acid sequence in the application in order to satisfy the written description requirements. Therefore, Applicants respectfully request that this rejection be withdrawn.

Claims 1-16 and 33-34 are further rejected under 35 U.S.C. §112, first paragraph, "as failing to comply with the enablement requirement."

Specifically, claims 1-16 and 33-34 are rejected "for incorporating essential material, PSMA, only by reference to publications."

Applicants respectfully traverse this rejection. As discussed above with regard to written description, because the amino acid sequence was known in the art at the time of filing, the recitation of the term PSMA is sufficient to satisfy the written description requirements.

Similarly, because the amino acid sequence of PSMA was known in the art, a skilled artisan could practice the claimed invention without undue experimentation. As such, the amino acid sequence of PSMA is not "essential material" as defined in section 608.01 of the MPEP. Therefore, the amino acid sequence does not need to be incorporated into the present application.

Claims 1-16 and 33-34 are also rejected "for lack of enablement for a method for determining is a subject is at risk for prostate cancer recurrence." In particular, the Office Action states that "the data disclosed in the instant specification only indicates that overexpression of the PSMA protein level is indicative of recurrent prostate cancer. The specification lacks confirmation of the marker predictive value in prospective population trials."

Applicants respectfully traverse this rejection. Applicants note that the claims as amended recite that the sample is from a subject diagnosed with prostate cancer. Applicants have clearly provided sufficient evidence of the correlation of between PSMA expression levels and risk of recurrence in subjects diagnosed with prostate cancer.

Applicants have demonstrated that PSMA expression is an independent predictor of prostate cancer recurrence. The present application describes a multivariate analysis of biopsy samples from one hundred and thirty six patients who underwent a radical prostectomy, determined PSMA expression levels at the time of the prostectomy and tracked those patients to determine which patients had prostate cancer recurrence. From this data, Applicants were able to demonstrate that PSMA expression levels at the time of diagnosis significantly differ between patients that later have recurrence and those who do not.

Applicants submit herewith a press release by a company unrelated to the Applicants that discusses the data presented in the present application and states that "we believe that the publication of clinical data showing overexpression of PSMA in primary cancer ... independently predicts disease recurrence." See the Cytogen Corporation Press Release dated January 5, 2004 and submitted herewith as Exhibit A.

The correlation between PSMA expression levels and prediction of prostate cancer recurrence has also been corroborated by others. For example, Perner et al. (2007) Human Pathology 38:696-701, submitted herewith as Exhibit B, performed univariate and multivariate

analysis of PSMA expression levels on biopsy samples from patients diagnosed with prostate cancer. This study evaluated 450 patients with prostate cancer. Consistent with the data provided in the present application, Perner et al. report that "high PSMA levels were associated with significant increase in PSA recurrence ... [and] this was independent of clinical parameters."

Therefore, Applicants submit that there is sufficient evidence to support the claimed methods.

The Office Action cites several references to support the allegation that the claimed methods are not enabled. Specifically, the Office Action cites Oesterreich et al., Tockman et al. and Vandesompele et al. Oesterreich et al. is cited as teaching "that **false positives correlation** can be obtained when **using the univariate analysis** to obtain a correlation of a marker with its prognostic value." As Applicants established the predictive value of PSMA expression to prostate cancer recurrence via **multivariate analysis**, the relevance of this statement is unclear.

With regard to the Tockman et al. and Vandesompele et al. references, both of these references are directed to completely different proteins for completely different disorders. Even more importantly, both of these references are analyzing proteins as **predictive markers for early detection of primary cancers** and not for **recurrence in a patient population diagnosed with a cancer**. All of the statements made in the Office Action regarding these references relate to "early stage markers", "the plausibility as markers of preclinical cancer" and confirmation on "prospective population trials". However, the claimed methods are not directed to early stage detection methods. Instead, the claimed methods are for determining risk of recurrence in a patient population that has been diagnosed with prostate cancer. Therefore, references related to a different kind of marker –one for early detection of primary cancers—is not relevant to the predictability of the claimed methods. The data provided in the present application and corroborated by subsequent reports is sufficient to demonstrate the predictability of the claimed methods.

For the reasons provided above, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §102(b)

Claims 1-3, 7-9 and 11-16 are rejected under 35 U.S.C. §102(b) as "being anticipated by Rosenthal S A et al, 2001 (Techniques in Urology, 7(1):27-37)." In particular, the Office Action alleges that

> Rosenthal et al teach that using an antibody to PSMA labeled with In 111 (or capromab pendetide), the positive predictive value (PPV) is 50% for prostatic fossa recurrence, and 62% for lymph node metastasis (abstract, tables 1-2 on pages 28-29). Rosenthal et al teach normal biodistribution of the labeled antibody imaging is in figure 1, and increased uptake of labeled antibody in prostatic fossa after prostatectomy is in figure 2, wherein local recurrence is confirmed by biopsy (p29, second column, last paragraph). Rosenthal et al. teach that capromab pendetide imaging for evidence of metastasis provides prognostic information regarding which patients are most likely to benefit from postprostatectomy radiation therapy. ... Rosenthal et al. teach that for a patient with recurrent disease following primary therapy, the predictive value of capromab pendetide imaging of prostate or prostate fossa, however, is limited due to lack of sensitivity of prostatic fossa biopsies; but providing valuable information when utilized along with other clinical, laboratory and available pathological information. ... All the limitations are met.

Applicants respectfully traverse this rejection. The claims of the present application are directed to methods of determining if a subject is at risk for prostate cancer recurrence which include providing a sample from a subject diagnosed with prostate cancer and determining PSMA expression levels in the sample, wherein increased PSMA expression levels relative to a reference standard that is statistically significant between subjects having recurrence and subjects that do not have recurrence indicate a risk of prostate cancer recurrence.

Rosenthal et al. do not teach or suggest the claimed methods.

Rosenthal et al. disclose methods of *in vivo* imaging with an indium labeled anti-PSMA antibody to diagnose prostate cancer or as part of a diagnosis of prostate cancer recurrence. Thus, Rosenthal et al. disclose determining the presence of a cancer either at the initial occurrence or upon indication of recurrence. For example, at page 28, Rosenthal et al. provide that capromab pendetide "may be utilized either ***at the time of initial diagnosis*** or ***in the setting of suspected recurrent disease.***" (***emphasis added***). Thus, Rosenthal et al. relates to the

diagnosis of existing prostate cancer and not a method for predicting the risk of prostate cancer recurrence.

In addition, Rosenthal et al. do not teach or suggest a method that includes obtaining a sample from the subject or determining the expression level of PSMA in the sample. Instead, Rosenthal et al. disclose *in vivo* imaging for PSMA expressing cells. No sample is obtained. Moreover, Rosenthal et al. do not teach or suggest quantifying the amount of PSMA expression. The methods of Rosenthal et al. are for imaging where potentially cancerous cells are present in the body and not for quantifying levels of PSMA expression. See, for example, page 33, second column, first full paragraph, "the potential benefit of capromab pendetide immunoscintigraphy is that it may be able to differentiate locally recurrent disease from regional or distant metastases, and it may be able to provide information about the anatomical location of disease."

For the reasons discussed above, Rosenthal et al. do not teach or suggest the claimed methods. Applicants respectfully request that this rejection be withdrawn.

Claims 1-3, 5-6 and 11-16 are rejected under 35 U.S.C. §102(b) as "being anticipated by Murphy et al, 1998 (Urology, 51:89-97)." In particular, the Office Action alleges

> Murphy et al teach that the PSMA value well above the normal range from 1 to 4 years postoperatively corresponds best with poor prognosis or suspected post-operative recurrence (p.92, first column, last four lines bridging second column). Murphy et al teach that the PSMA in serum sample is detected using Western blot, and that all patient samples are assessed against a healthy normal donor sample, and a prostate cancer sample with a high PSMA from the same Western blot as standard control (p.90, first column, item under PSMA assay). Murphy et al teach that the serum is from a population of patients from a screening group, a difficult to diagnostic group, a pre- and postoperative radical prostectomy, and from a group with metastatic disease, which population is followed for a serial period.

Applicants respectfully traverse this rejection. The claimed methods are directed to methods of determining if a subject is at risk for prostate cancer recurrence.

Murphy et al. disclose PSMA levels at various stages of prostate cancer and disclose the PSMA levels increase as the disease progresses. Murphy et al., however, do not teach or suggest that at any particular stage of the disease there can be statistically significant variation between

the patients at that stage to assess the risk of recurrence in a subset of the patients. Thus, nothing in the Murphy et al. references teaches the claimed methods. Therefore, Applicants respectfully request that this rejection be withdrawn.

The fees in the amount of $1020 for the Petition for Extension of Time are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 10448-201001.

Respectfully submitted,

Date: June 12, 2007

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